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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,046	11/20/2001	Frederic J. de Sauvage	P1405R1C1	1433

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GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 04/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,046	DE SAUVAGE ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 1/13/06 has been entered in full. Claims 29-33, 39-43 and 49 are amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 29-54 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (7/12/2005).

The objection to the specification at pg 2 is *withdrawn* in view of Applicants' amendment to the specification.

The objection to claims 29, 30, 39, 40 and 49 at pg 3 is *withdrawn* in view of Applicants' amendment to the claims.

The rejection of claims 29, 31-39 and 41-48 under 35 U.S.C. § 112, first paragraph at pg 3-6 for failing to provide enablement is *withdrawn* in view of Applicants' amendments to the claims and Applicants' persuasive arguments.

The rejection of claims 29, 31-39 and 41-48 under 35 U.S.C. § 112, first paragraph at pg 7-9 for lacking written description is *withdrawn* in view of Applicants' amendments to the claims and Applicants' persuasive arguments. However, please see the new rejection under 35. U.S.C. § 112, first paragraph below, for new matter, necessitated by Applicants' amendments to the claims.

The rejection of claims 39-48 under 35 U.S.C § 112, second paragraph, at pg 9-10 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn in part* in view of Applicants' amendments to the claims. Specifically, Applicants have amended claim 39 to change "*Smoothened*" to the "*Smoothened* polypeptide", which clarifies that the term refers to the *Smoothened* polypeptide but not the *Smoothened* gene. However, the rejection is

only withdrawn in part because Applicants have not addressed the other basis of rejection of claims 29 and 39 under 112, 2nd paragraph that was set forth previously (see below in the section – Claim Rejections – 35 USC § 112, 2nd paragraph).

Please see new claim rejections, below.

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

Claims 29-50 and 52-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

Claims 29 and 39 each recite, "a purified antibody which specifically binds to a patched-2 polypeptide (1) SEQ ID NO: 2..." In support of the amended claim, Applicants point to pg 49, lines 7-8. However, page 49, lines 7-8 refers to "preparation of monoclonal antibodies which can specifically bind vertebrate *patched-2*". The term "*patched-2*" is defined by the specification on pg 5, lines 5-9 to encompass "*patched-2* variants (which are further defined herein) having *patched-2* biological activity." Polyclonal antibodies are discussed on page 23, lines 6-17. However, nowhere does the specification teach a polyclonal antibody that "specifically binds" to *patched-2*. There is no conception of the specific genus of polyclonal antibodies that "specifically bind" to SEQ ID NO: 2 (or variants), nor does the concept of the specific genus flow naturally from the disclosure of the specification. Therefore, the specification as originally filed lacks support for claims that encompass said polyclonal antibodies. Each of claims 29-34, 36-44, 46-50 and 52-54 encompasses a polyclonal antibody that "specifically binds" to SEQ ID NO: 2 (or variants thereof). Therefore each of claims 29-34, 36-44, 46-50 and 52-54 contains new matter.

Claims 29 and 39 each recite, "SEQ ID NO: 2 or a variant thereof having 1 to 5 conservatively substituted, added or deleted amino acid residues..." In support of the amended claim, Applicants point to pg 11, lines 22-27. However, page 11, lines 22-27, refer only to single amino acids substitutions, or "insertions or deletion may optionally be

in the range of 1 to 5 amino acids." Lines 15-16 refer to "variations may be a substitution, deletion or insertion of one or more codons." Nowhere does the specification teach conservative substitutions of 1 to 5 amino acids of SEQ ID NO: 2. This concept is not expressly asserted nor does it flow naturally from the specification. Therefore, the specification as originally filed lacks support for the genus of molecules encompassed by each of amended claims 29 and 39. Claims 30, 34-38, 40 and 44-48 depend from either 29 or 39 and include the same limitation. Therefore, these claims also contain new matter.

Claim Rejections - 35 USC § 112, 2nd paragraph

Claims 29-54 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 and 39 are indefinite because it is unclear if the phrase "and (2) which binds to hedgehog" (or "Smoothened") refers to the purified antibody or to the patched-2 polypeptide.

This rejection was set forth at pg 9 of the 7/12/2005 Office Action. In the 1/13/2006 response, Applicants refer to the rejection of claims 29 and 39, but then only address the rejection of claim 39 with regards to whether *Smoothened* refers to the gene or polypeptide (which was a separate issue from the above rejection of the claims). Furthermore, the 1/13/2006 claim amendments do not render the claims definite. In this regard, claim 29 would be rendered definite if amended, for example, to recite, "...a purified antibody which specifically binds to a *patched-2* polypeptide of SEQ ID NO: 2 or variant thereof ... and wherein said *patched-2* polypeptide binds to hedgehog polypeptide".

The following new rejections under 35 U.S.C. § 112, second paragraph are necessitated by Applicants' amendments to the claims.

The term "specifically" in claims 29, 39, and 49 is a relative term which renders the claim indefinite. The term "specifically" is not defined by the claim, the specification

does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The degree of binding of the antibody to SEQ ID NO: 2 is rendered indefinite by use of the term "specifically". The specification does not provide a limiting definition of the term "specifically binds". The specification only refers to "monoclonal antibodies which can specifically bind vertebrate *patched-2*." This teaching does not clarify whether or not an antibody that specifically binds to SEQ ID NO: 2 can bind to other proteins or not. Does specific binding mean that the antibody binds SEQ ID NO: 2 but bind to no other polypeptides? Or that it binds to SEQ ID NO: 2 with a greater specificity than other proteins. If so, neither the specification nor the claims clarify what degree of binding is sufficient to meet the limit of "specifically binds". For purposes of prosecution, the claim has been interpreted broadly to encompass any antibody that binds to any protein.

Claim 29 is indefinite because it recites the phrase, "conservatively substituted, added or deleted amino acid". It is unclear what is a conservatively added amino acid, or a conservatively deleted amino acid.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 103

Claims 29-33, 35-43, 45-49 and 51-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motoyama et al. 18 February 1998. Nat Genet. 18(2): 104-6 in view of Tso et al, U.S. Patent No. 5,932,448, published 3 August 1999, and filed 11/29/1991. This rejection was set forth at pg 10-11 of the 7/12/2005 Office Action.

Claims 29-33, 39-43 and 49 encompass any antibody that specifically binds to a patched-2 polypeptide of instant SEQ ID NO: 2. The remaining claims encompass any monoclonal (claims 35, 45 and 51), humanized (claims 36, 46 and 52), bispecific (claims 37, 47 and 53), or heteroconjugated (claims 8, 48 and 54) antibody that specifically binds to a patched-2 polypeptide.

Motoyama teaches the mouse gene *Ptch2* that encodes the polypeptide patched-2. The sequence of the mouse patched-2 polypeptide is 89.3% similar to instant SEQ ID

NO: 2 (which is the human patched-2 polypeptide). An alignment of the two sequences is attached was attached to the 7/12/05 Office Action as Sequence Alignment #1. Motoyama does not teach an antibody to the mouse patched-2 polypeptide.

Tso teaches general methods for producing bispecific antibodies (col 1, line 62-67). Tso further teaches monoclonal antibodies for use in production of bispecific antibodies (col 7, line 19). Tso further teaches humanized antibodies for use in bispecific antibodies (col 2, lines 46-47). The instant specification defines heteroconjugated antibodies as "antibodies composed of two covalently joined antibodies (pg 26). Tso teaches chemical cross-linking of two antibodies to produce a bispecific antibody (col 1, lines 34-35). This bispecific antibody taught by Tso meets the definition of a "heteroconjugated" antibody as defined by the specification.

It would be obvious to the person of ordinary skill in the art at the time the invention was made to make antibodies as taught by Tso to the mouse patched-2 polypeptide taught by Motoyama. The person of ordinary skill in the art would be motivated to do so because Tso teaches that the antibodies have general uses applicable for use with any protein, such as cross-linking a horseradish peroxidase for purposes of detection (see col 11, lines 52-55). The person of ordinary skill in the art would have expected success because Motoyama teaches the sequence of mouse patched-2 polypeptide, and Tso teaches the methods necessary to produce antibodies to any protein sequence.

Due to the high degree of similarity between the two sequences, including numerous regions of 20 or more amino acids with 100% identity between the sequences, one of skill in the art would reasonably predict that numerous monoclonal antibodies, including bispecific, humanized, and heteroconjugated antibodies, made to mouse patched-2 polypeptide as taught by Motoyama would specifically bind to the human patched-2 polypeptide of instant SEQ ID NO: 2.

Applicants' arguments (1/13/06; pg 8-9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response dated 1/13/06, Applicants submit that claims 29, 39 and 49 have been amended to recite that the antibodies specifically bind SEQ ID NO: 2. Applicants argue that the "hypothetical antibodies asserted in the Examiner's arguments would not be specific to SEQ ID NO: 2". Applicants request reconsideration and withdrawal of the rejection.

Applicants' arguments have been fully considered but are not found persuasive for the following reasons. Applicants argue that antibodies specific to the mouse *patched-2* sequence taught by Motoyama would not be specific to SEQ ID NO: 2. This has been fully considered but is not found persuasive. The specification does not define the phrase "specifically binds" and therefore the term has been broadly interpreted to encompass any degree of binding (see Claim Rejections – 35 USC 112, 2nd paragraph). Furthermore, the specification does not teach antibodies that "specifically bind" to SEQ ID NO: 2 but not to other vertebrate patched-2 sequences. The specification does not define any epitopes of SEQ ID NO: 2 that exist where an antibody would bind that would not bind to any region of mouse *patched-2*. Instead, the specification only teaches monoclonal antibodies that specifically bind to "vertebrate patched-2" (pg 48, lines 7-8, "preparation of monoclonal antibodies, which can specifically bind vertebrate patched-2"). Therefore, monoclonal antibodies that bind to a mouse-2 patched polypeptide (as taught by Motoyama) and also cross-react with a patched-2 polypeptide of SEQ ID NO: 2 (as described above) would be encompassed by the genus of antibodies that "specifically bind" to SEQ ID NO: 2.

Claims 29, 34, 39, 44, 49 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motoyama et al. 18 February 1998. Nat Genet. 18(2): 104-6, in view of Liddell et al. Antibody Technology, BIOS Scientific Publishers, 1995. Pgs 9-24 and 85-102. This rejection was set forth at pg 11-12 of the 7/12/2005 Office Action.

Claims 29, 39 and 49 encompass any antibody that specifically binds to a patched-2 polypeptide of instant SEQ ID NO: 2. Claims 34, 44, and 50 encompass any polyclonal antibody that specifically binds to a patched-2 polypeptide of instant SEQ ID NO: 2.

Motoyama teaches the mouse gene *Ptch2* that encodes the polypeptide patched-2. The sequence of the mouse patched-2 polypeptide is 89.3% similar to instant SEQ ID NO: 2 (which is the human patched-2 polypeptide). An alignment of the two sequences was attached to the 7/21/05 Office Action as Sequence Alignment #1. Motoyama further teaches the *in situ* expression of the mouse gene *Ptch2* in the mouse "developing tooth, hair follicle and whisker" (see Figure 2). Motoyama does not teach polyclonal antibody to the mouse patched-2 polypeptide.

Liddell teaches general methods for producing polyclonal antibodies to any protein sequence for use (see pgs 9-24) and the specific use of polyclonal antibodies in immunocytochemistry (see pg 86).

It would be obvious to the person of ordinary skill in the art at the time the invention was made to make polyclonal antibodies for immunocytochemistry as taught by Liddell to the mouse patched-2 polypeptide taught by Motoyama. The person of ordinary skill in the art would be motivated to do so in order to determine the *in situ* expression of the mouse patched-2 polypeptide taught by Motoyama. The person of ordinary skill in the art would have expected success because Motoyama teaches the sequence of mouse patched polypeptide and *in situ* expression of the nucleic acid, and Liddell teaches the methods necessary to produce polyclonal antibodies to any protein sequence and the methods to use the antibodies in immunocytochemistry.

Due to the high degree of similarity between the two sequences, including numerous regions of 20 or more amino acids with 100% identity between the sequences, one of skill in the art would reasonably predict that numerous polyclonal antibodies made to mouse patched-2 polypeptide as taught by Motoyama would specifically bind to the human patched-2 polypeptide of instant SEQ ID NO: 2.

Applicants' arguments (1/13/06; pg 8-9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons. In the response dated 1/13/06, Applicants submit that claims 29, 39 and 49 have been amended to recite that the antibodies specifically bind SEQ ID NO: 2. Applicants argue that the "hypothetical antibodies asserted in the Examiner's arguments would not be

specific to SEQ ID NO: 2". Applicants request reconsideration and withdrawal of the rejection.

Applicants' arguments have been fully considered but are not found persuasive for the following reasons. Applicants argue that antibodies specific to the mouse *patched-2* sequence taught by Motoyama would not be specific to SEQ ID NO: 2. This has been fully considered but is not found persuasive. The specification does not term define the phrase "specifically binds" and therefore the term has been broadly interpreted to encompass any degree of binding (see Claim Rejections – 35 USC 112, 2nd paragraph). Furthermore, the specification does not teach antibodies that "specifically bind" to SEQ ID NO: 2 but not to other vertebrate patched-2 sequences. The specification does not define any epitopes of SEQ ID NO: 2 that exist where an antibody would bind that would not bind to any region of mouse *patched-2*. Instead, the specification only teaches monoclonal antibodies that specifically bind to "vertebrate patched-2" (pg 48, lines 7-8, "preparation of monoclonal antibodies, which can specifically bind vertebrate patched-2"). Therefore, polyclonal antibodies that bind to a mouse-2 patched polypeptide (as taught by Motoyama) and also cross-react with a patched-2 polypeptide of SEQ ID NO: 2 (as described above) would be encompassed by the genus of antibodies that "specifically bind" to SEQ ID NO: 2.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER